REMARKS

Prior to the entry of the present amendment, claims 1-24 are pending. Claims 1, 2, 7, 8, 13, 14, 16-21, 23, and 24 are rejected under 35 U.S.C. §112, second paragraph; claims 16, 17, 21, and 24 are rejected under 35 U.S.C. §101; claims 1-24 are rejected under 35 U.S.C. §102; claims 1-24 are rejected under 35 U.S.C. §103; and claims 1-7 and 15-21 are rejected for nonstatutory obviousness-type double patenting. Applicants address each of these rejections as follows.

Claim amendments

Claim 18 has been amended and new claims 25-35 have been added. Claims 1-17 and Claims 19-24 are cancelled. Support for the amendment to claim 18 is found, for example, at page 3, lines 9-36, of the specification. Support for new claims 25-35 is found throughout the present specification, for example, at page 1, lines 8-10, page 2, lines 20-36, page 3, lines 9-36, page 4, lines 33 and 34, page 5, lines 29-30, and page 8, lines 11-17.

Support of the recitation of "non-cytotoxic folate" is found, for instance, in Examples 1-5 where Applicants describe conjugation of folic acid to an antibody and coupling a radionuclide to the folic acid/antibody complex. Applicants note that folic acid is a dietary supplement and is, for example, given to pregnant women. As such, Applicants submit that folic acid is recognized as being non-cytotoxic.

No new matter has been added by the present amendment. Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1, 2, 7, 8, 13, 14, 16-21, 23, and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office objects to claim 1 for reciting a "broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim)," for including the term "e.g.," and for reciting the term "folate derivatives." The Office objects to claim 7 for reciting a "broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim)," for including the term "e.g.," for reciting the term "standard procedures," and for omitting essential steps of the claimed method. Claim 8 is included in this basis for rejection for failing to specify what matter the phrase "fragment or construct" relates to. Claim 13 is rejected as indefinite for recitation of the phrase "polyclonal antibody from other species." Claims 14 and 18-20 are rejected as indefinite for a lack of antecedent basis for the phrase "the folate binding protein." Claims 16, 17, and 21 are rejected as indefinite for not specifying the steps involved in the method/process claimed. Claim 24 is rejected as indefinite for lack of antecedent basis, for recitation of the term "e.g.," and for omitting essential steps of the claimed method.

Claims 1-17 and 19-24 have been canceled. As such, the 35 U.S.C. § 112, second paragraph rejection of these claims is moot. Applicants submit that claim 18 as amended, and new claims 25-35 are free of these bases for rejection.

Rejection under 35 U.S.C. § 101

Claims 16, 17, 21, and 24 are rejected under 35 U.S.C. §101 because the "claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of process..." (Office Action, page 5). Claims 16, 17, 21, and 24 have been cancelled and, therefore, the rejection of these claims is moot. Applicants submit that claim 18, as amended, and new claims 25-35 are free of the 35 U.S.C. §101 rejection.

Rejection under 35 U.S.C. § 102

Claims 1-24 are rejected under 35 U.S.C. § 102(b) as anticipated by Sinkule et al. (EP 282057; hereafter "Sinkule"), and claims 1, 7, 8, 14, 16-21, and 24 are rejected under 35 U.S.C. § 102(b) as anticipated by Niswender et al. (U.S. Patent No. 4,366,185; hereafter "Niswender"). Applicants address these bases for rejection, as directed to the present claims, in turn below.

With regard to Sinkule, the Office states (page 6):

> Sinkule et al. (EP 282057) teaches of a receptor binding conjugate comprising three components, 1.) an antibody, 2.) a radionuclide and 3.) a chemotherapeutic agent, such as folate or analogues thereof. The antibody

> may be a monoclonal or polyclonal or variations thereof used for a wide variety of target antigens. Methods of making conjugates, using linkers, etc. are set forth ... Various radionuclides are disclosed ... The therapeutic agent chosen for use will vary according to the nature of the disease to be treated and the type of target cells to be eradicated *in vivo* within human or mammalian host. The conjugate can be administered by any conventional method, such as intravenously and the pharmaceutical agents may be in various pharmaceutical compositions with various combinations of materials therefore, which would encompass the kits, as claimed. (Citations omitted.)

Applicants note that the present claims recite a conjugate that contains (1) an antibody, antibody fragment or antibody construct, (2) a *non-cytotoxic* folate, and (3) a radionuclide. Sinkule fails to describe a conjugate containing these three components. Instead, Sinkule describes complexes containing *toxic* folic acid derivatives (i.e., methotrexate) as chemotherapeutic agents (see, e.g., column 2, lines 50-53). As Sinkule does not describe every element of the presently claimed invention, Sinkule cannot anticipate claim 18 as amended and new claims 25-35. This basis for the § 102 rejection may be withdrawn.

Turning to the anticipation rejection over Niswender, the Office states (page 7):

> Niswender (US 4,336,185) teaches of a receptor binding conjugate comprising three components, 1.) an antibody (e.g. gamma globulin, aka, immunoglobulin), 2.) a radionuclide or radionuclides and 3.) folic acid and salts, esters, and amides thereof (abstract, column 1, lines 3-6). Methods of making the conjugates are disclosed in column 2-3.

Applicants respectfully disagree with the Office's characterization of Niswender. Niswender describes proteins conjugated to folates (see column 1, lines 17-37) and radiolabeled folates for use *in vitro* folate assays (see column 1, line 40, to column 2, line

7). Niswender fails to describe a method of targeting a radionuclide to a malignant cell in a subject using a conjugate having (1) an antibody, antibody fragment or antibody construct with affinity to a tumor associated antigen, (2) a non-cytotoxic folate, and (3) a radionuclide (claim 18) or a conjugate containing (1) a radionuclide, (2) an antibody, antibody fragment or antibody construct, with affinity for a tumor associated antigen, *and* (3) at least one non-cytotoxic folate (claim 31). As such, Niswender fails to describe all elements of the presently claimed invention. Applicants submit that claim 18 as amended and new claims 25-35 are free of this basis for rejection.

Rejection under 35 U.S.C. § 103

Claims 1-24 are rejected under 35 U.S.C. 103(a) as obvious over Griffiths et al. (U.S. Patent No. 6,077,499; hereafter "Griffiths") in view of Goldenberg et al. (U.S. Patent No. 5,698,178; hereafter "Goldenberg"). The Office states (pages 7 and 8):

> Griffiths et al. (US 6,077,499) discloses a receptor binding conjugate comprising a targeting moiety (e.g. an antibody or fragment thereof), one or more therapeutic agents and folic acid derivatives where the therapeutic agents may be a radionuclide or mixtures thereof ... Griffiths et al. (US 6,077,499) does not disclose that the conjugates may be prepared in kits having separate container/vials or the use of all the same antibodies as the instant claims, e.g. humanized antibodies.
>
> * * *
>
> Goldenberg et al. (US 5,698,178) discloses receptor binding conjugates which comprise various antibodies and at least one diagnostic or therapeutic agent. The diagnostic and therapeutic agents include radionuclides and folic acid analogues. (Citations omitted.)

Applicants, for the reasons detailed below, respectfully submit that the present claims are free of this basis for rejection.

The M.P.E.P. (§ 2143), citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991), requires that, to establish a *prima facie* case of obviousness:

> [T]he prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. (Emphasis added.)

The cited references, alone or in combination, fail to meet this standard.

Griffiths, as noted in the abstract, describes a tumor therapy method involving two conjugates; namely, "a first conjugate comprising a targeting moiety, a first member of a binding pair, and a first therapeutic agent... [and] a second conjugate comprising a complementary member of the binding pair and a second therapeutic agent," where the second therapeutic agent may be the same or different as the first therapeutic agent. Griffiths includes folic acid analogs in lists of cytotoxic agents (see, e.g., column 8, lines 39-63). Griffiths not only fails to teach or suggest a single conjugate containing (1) an antibody, antibody fragment or antibody construct, (2) a non-cytotoxic folate, and (3) a radionuclide, but also fails to teach or suggest making a conjugate with a non-cytotoxic folate.

Goldenberg does not remedy this deficiency. While Goldenberg describes conjugates containing folic acid analogs, these folic acid analogs are described as

chemotherapeutic agents (see, e.g., column 23, lines 55-60). Chemotherapeutic agents are toxins that kill cells. Clearly any folic acid analogs described by Goldenberg are not non-cytotoxic folates. Moreover, Goldenberg fails to make any suggestion to generate a conjugate containing a non-cytotoxic folate or that there would be any benefit in doing so.

In short, Griffiths and Goldenberg, even when combined, fail to describe or suggest a conjugate containing (1) an antibody, antibody fragment or antibody construct, (2) a *non-cytotoxic* folate, and (3) a radionuclide. As such, the cited art does not support a *prima facie* case for obviousness of the presently claimed invention. Applicants submit that claim 18 as amended and new claims 25-35 are free of the § 103 rejection over Griffiths and Goldenberg.

Obviousness-type double patenting

Claims 1-7 and 15-21 are rejected for nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent No. 6,740,304 B2 ("the '304 patent") in view of Sinkule. The Office states (page 9):

> The exact method of delivery of therapeutic radiation comprising an antibody, folate, and radionuclide for binding to malignant cells, such as brain, lung, etc. is disclosed in US 6,740,304 B2 as well as the radionuclides (^{125}I) of the instant claims.

Applicants respectfully disagree.

The methods of claims 1-6 of the '304 patent are directed to delivering therapeutic radiation to a patient with *a malignant cell expressing a folate binding protein*. These

methods involve administering to the patient a conjugate containing (1) an *inert* human IgG or IgM antibody or antibodies or a fragment or construct thereof, (2) a radionuclide or a mixture of radionuclides, and (3) *a folate that binds to the folate binding protein.* In contrast, claim 18, as amended is directed to a method of targeting a radionuclide to a malignant cell within a subject, where the *malignant cell expresses a tumor associated antigen* and expresses folate binding protein. The method includes the step of coupling an antibody, antibody fragment, or antibody construct *having affinity for the tumor associated antigen* to at least one non-cytotoxic folate to form *a dual binding conjugate.* Given that claims 1-6 of the '304 patent recite conjugates containing an inert antibody, these claims clearly fail to teach or suggest a dual binding conjugate containing an antibody having affinity for a tumor associated antigen and a non-cytotoxic folate. Nothing in Sinkule teaches or suggests modifying the conjugates recited in claims 1-6 of the '304 patent to arrive at the conjugates recited in the present claims.

With regard to claim 31, Applicants submit that claims 1-6 of the '304 patent and Sinkule also fail to provide any teaching, suggestion, or motivation to generate a conjugate containing (1) a radionuclide, (2) an antibody, antibody fragment or antibody construct, *with affinity for a tumor associated antigen*, and (3) at least one *non-cytotoxic* folate.

For all the above reasons, Applicants submit that the present claims are nonobvious over the combination of claims 1-6 of the '304 patent and Sinkule. This basis

for rejection should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a petition to extend the period for replying to the Office Action for three (3) months, to and including January 5, 2007, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 5 January 2007

Paul T. Clark
Reg. No. 30,162

JAN M. TITTEL, Ph.D.
Reg. No. 52,290

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045